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Novel approach to 6-alkenyl-substituted pyridoxine derivatives based on the Heck reaction

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ABSTRACT

A new synthetic approach to 6-alkenyl-substituted pyridoxine derivatives was developed based on the Heck reaction. The reaction, which was catalyzed using a mixture of $\text{Pd}(\text{OAc})_2$, $(o\text{-Tol})_3\text{P}$ and Bu_3N as a base, led to seven new 6-alkenyl pyridoxine derivatives. When acrylic acid was used the products of decarboxylation and dimerization were formed.

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Introduction

The Heck reaction is widely used as a reliable tool for obtaining biologically active structures with double bonds on both laboratory and industrial scales due to its regio- and stereoselectivity, availability of initial reagents, and adjustable reaction conditions [1]. On industrial scales, the Heck reactions of variously substituted pyridines are widely used for the synthesis of pharmaceutical substances [2]. For example, the Heck reactions of 3-hydroxy-6-bromopyridines, which can be considered as structural pyridoxine congeners, are successfully applied in the synthesis of HIV-1 inhibitors [3] or serotonin 5-HT₄-receptors agonists [4].

Derivatives of pyridoxine (vitamin B₆) substituted at various positions of the pyridine ring represent interesting molecular structures with rich bioactivity potential. In particular, pyridoxine derivatives with various alkenyl substituents on the pyridine ring have been reported as promising antitumor agents [5]. Several 6-alkenyl-substituted pyridoxine derivatives containing stilbene-like structural motifs exhibited antitumor activity against the MCF-7 (breast cancer) cell line and possess selective estrogen receptor modulating activity [6]. A number of 2-methyl-3-hydroxy-6-alkenyl-substituted pyridine derivatives structurally related to pyridoxine have been described as potential antitumor agents acting via modulation of ROR γ [7] and S1P1 [8] receptor activity.

A common synthetic approach to alkenyl derivatives of pyridoxine is the Wittig reaction [5,6]. However, this strategy has several drawbacks, such as laborious multi-step approaches to the

initial phosphonium salts, formation of *E/Z*-diastereomeric mixtures which necessitates chromatographic separation, and difficult purification from triphenylphosphine oxide.

To the best of our knowledge, only one example of the Heck reaction for the synthesis of 6-alkenyl-substituted derivatives has been reported to date [9]. The main feature of this synthesis was utilization of the 6-vinyl derivative of pyridoxal as a starting reagent. This approach might be troublesome for scaling-up as it involves a five-step procedure including one Grignard reaction, which requires low temperatures and an inert atmosphere.

In this work, a convenient three-step synthetic approach to 6-alkenyl-substituted pyridoxine derivatives based on the Heck reaction of a 6-bromo pyridoxine derivative was developed. The reaction, which was catalyzed using a mixture of $\text{Pd}(\text{OAc})_2$, $(o\text{-Tol})_3\text{P}$ and Bu_3N as a base, successfully led to seven new 6-alkenyl-substituted pyridoxine derivatives.

Results and discussion

The key pyridoxine-containing reactant for the Heck reaction was synthesized in two steps from commercially available reagents (Scheme 1). In the first step, compound **1** was synthesized from pyridoxine hydrochloride according to the previously reported method [10]. Bromination of the protected pyridoxine derivative **1** with *N*-bromosuccinimide (NBS) in DMF for 1 h at room temperature led to the target bromide **2** in 75% yield.

Initially, the Heck reaction conditions were optimized using compound **2** and methyl acrylate as model substrates (Table 1, Scheme 2).

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